A STUDY TO EVALUATE THE PHARMACOKINETICS OF SKELAXIN® (METAXALONE) 2x400 MG TABLET ADMINISTERED TO YOUNG AND ELDERLY VOLUNTEERS UNDER FED AND FASTED CONDITIONS

ELN151607-105

CLINICAL STUDY REPORT

IND Number:

Name of Product:	Skelaxin® (metaxalone)
Phase of Development:	Phase I
Date Study Initiated:	April 9, 2002
Date of Last Observation:	May 20, 2002
Design:	Single center, open label, single dose, randomized, two-period, two way cross-over trial in volunteers
Sponsor:	Elan Pharmaceuticals, Inc. 7475 Lusk Boulevard San Diego, CA 92121
Principal Investigator:	Mark J. Allison, M.D. MDS Pharma Services 4639 South 36th Street Phoenix, AZ 85040 Tel: (602) 437-0097
Prepared by:	PRACS Institute, Ltd.
Date of Report:	April 16, 2003

This study was performed in accordance with Good Clinical Practice guidelines. The final study report incorporates ICH 1996 Guidelines and is archived at Elan Pharmaceuticals, Inc.

SIGNATURE PAGE

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Sponsor Name: Elan Pharmaceuticals, Inc.
Document Version: 1

Prepared at PRACS Institute, Ltd. by:

Brenda L. Krogen, M.S.
Statistics Coordinator — Date: 04/16/03

Reviewed at MDS Pharma Services by:

Mark J. Allison, M.D.
Principal Investigator — Date: 18 Apr 03

Reviewed by Quality Assurance at PRACS Institute, Ltd. by:

Thomas E. Ary, Ph.D.
Director, Quality Assurance — Date: 04/16/03

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Approved by:

Michael C. Scaife, Ph.D.
Vice President, Global Regulatory Affairs — Date: April 21 2003

SIGNATURE PAGE

A STUDY TO EVALUATE THE PHARMACOKINETICS OF SKELAXIN® (METAXALONE) 2x400 MG TABLET ADMINISTERED TO YOUNG AND ELDERLY VOLUNTEERS UNDER FED AND FASTED CONDITIONS

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Sponsor Name: Elan Pharmaceuticals Inc

This is to certify that Quintiles (10245 Hickman Mills Drive, P.O. Box 9708, Kansas City, MO 64134-0708) has made a comparison of the pharmacokinetics parameters calculated by PRACS in Appendices 16.2.5.5 through 16.2.5.8 with those calculated independently by Quintiles. The original analysis by PRACS is considered to be acceptable and can be used as is.

Mark G. Eller, Ph.D.
Vice President, Clinical pharmacology

11 Apr 03
Date

2.0 SYNOPSIS

NAME OF COMPANY: Elan Pharmaceuticals, Inc.	INDIVIDUAL STUDY SYNOPSIS Page 1 of 3	
NAME OF FINISHED PRODUCT: Skelaxin®	INDIVIDUAL STUDY REFERRING TO PART OF DOSSIER Volume:	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF ACTIVE INGREDIENT: Metaxalone	Page:	

Title of Study:
A Study to Evaluate the Pharmacokinetics of Skelaxin® (metaxalone) 2x400 mg Tablet Administered to Young and Elderly Volunteers Under Fed and Fasted Conditions

Date of Protocol: March 28, 2002

Investigators:
Principal Investigator: Mark J. Allison, M.D.
Sub-Investigator: Irving E. Weston, M.D.

Study Centers:
MDS Pharma Services
4639 South 36th Street
Phoenix, AZ 85040
Tel: (602) 437-0097

Study Period:
Date of First Treatment: April 9, 2002
Date of Last Observation: May 20, 2002

Phase of Development:
Phase I

Primary Objective:
The primary objectives are to evaluate the effect of age and food on the pharmacokinetics of Skelaxin® (metaxalone) when administered to two different age groups.

Methodology: This study was a single center, open label, single dose, two-period (per age group), randomized, two way cross-over trial in young volunteers between the ages of 18-55 years old (average age 39.3 ± 10.8) and the elderly, 65 and older, (average age 71.5 ± 5). On Study Days 1 and 8, a single oral dose (2 x 400 mg) of Skelaxin® (metaxalone) was administered, once fed and once fasted, to each of the subjects. Blood sampling (19 per subject each period) for drug content analysis occurred within one hour prior to dosing (0 hour) and after dose administration on Days 1 and 8 at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36, and 48 hours.
Number of Subjects: Forty-eight healthy subjects were enrolled in the study (24 males, 24 females). Forty-four subjects successfully completed the study and were used for the pharmacokinetic and statistical analyses. The following subjects completed Period I but did not complete Period II, Subject 29 was dropped for elevated ALT and Subject 33 was dropped for anemia. Subject 34 did not return for Period II check-in, and Subject 45 was dropped on Day 3 of Period I due to non-compliance. All subjects who received treatment were included in the safety analysis.
Diagnosis and Main Criteria for Inclusion: Agreed to voluntarily participate and sign informed consent document; volunteers over the age of 18; within 20% of ideal body weight according to the Metropolitan Height and Weight Table; childbearing female subjects must not be pregnant or lactating and willing to use contraception.
Test Product, Dose, and Mode of Administration, Batch No.: Treatment A: 2 x 400mg Skelaxin® (metaxalone) with food Lot No.: 34851A, Exp.: 31-Jan-05 Treatment B: 2 x 400mg Skelaxin® (metaxalone) without food Lot No.: 34851A, Exp.: 31-Jan-05
Duration of Treatment: A single dose was administered on Study Day 1 and Study Day 8.
Reference Therapy, Dose, and Mode of Administration, Batch No.: None
Criteria for Evaluation: The following pharmacokinetic parameters were calculated for metaxalone: $AUC_{(last)}$, $AUC_{(inf)}$, C_{max}, T_{max}, K_{el} and $T_{1/2}$

Statistical Methods:
For each age and treatment group, descriptive statistics of plasma concentrations at each sampling time were reported. Descriptive statistics for the pharmacokinetic parameters were presented by age and treatment group as well. The age, treatment, and age-by-treatment effects for each pharmacokinetic parameter were tested using an ANOVA model with age, subject within age, treatment, and the age-by-treatment interaction as factors.

Summary of Results:

Pharmacokinetics:
During the study there were no protocol deviations to confound the pharmacokinetic and bioavailability analyses.

Young Subjects: Mean ± Standard Deviation for Non-Transformed Data

Parameter	Fed	Fasted
$AUC_{(last)}$	20482.38 ± 7645.11	19836.24 ± 7838.85
$AUC_{(inf)}$	20814.57 ± 7589.14	20489.57 ± 7910.28
C_{max}	2915.27 ± 1591.87	2719.02 ± 1237.54

Elderly Subjects: Mean ± Standard Deviation for Non-Transformed Data

Parameter	Fed	Fasted
$AUC_{(last)}$	24340.43 ± 11684.95	23797.04 ± 10623.52
$AUC_{(inf)}$	24704.17 ± 11662.03	24194.13 ± 10689.44
C_{max}	3680.21 ± 2161.75	3167.89 ± 1345.06

P-Values Based on Ln-Transformed Data

Effect	$AUC_{(last)}$	$AUC_{(inf)}$	C_{max}
Age	0.3589	0.3891	0.2037
Treatment	0.4353	0.5618	0.6988
Interaction	0.3986	0.4935	0.9600

There were no statistically significant differences detected for $AUC_{(last)}$, $AUC_{(inf)}$, or C_{max} based on age, treatment, or the interaction of age-by-treatment.

Safety:
A total of 54 adverse events were reported over the course of the study: 23 adverse events were considered unrelated by the investigator(s) and 31 adverse events were considered related to the study drug

Conclusions:
There were no statistically significant age effects detected for any of the pharmacokinetic parameters.

All study treatments were well tolerated by all subjects.

Date of Report: 04/16/03

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4.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event
$AUC_{(last)}$	Experimental area under the curve calculated to the last quantifiable concentration according to the linear trapezoidal rule
$AUC_{(inf)}$	Area under the curve extrapolated to infinity
CRF	Case Report Form
C_{max}	Maximum plasma concentration
CS	Clinically Significant
ECG	Electrocardiogram
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human Immunodeficiency Virus
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
K_{el}	Slope of the terminal linear portion of the concentration versus time curve
NCS	Not Clinically Significant
PK	Pharmacokinetic
QA	Quality Assurance
SAE	Serious Adverse Event
SD	Standard Deviation
$T_{1/2}$	Terminal half-life
T_{max}	Time to reach the maximum plasma concentration

5.0 ETHICS

5.1 Institutional Review Board (IRB)

Prior to the initiation of the study, the investigator sent the study protocol, consent and the Physician's Desk Reference Reprint to the MDS Pharma Services Institutional Review Board (IRB). The investigator obtained signed evidence of protocol and informed consent approval from the IRB and forwarded the approval letter to the Sponsor. MDS Pharma Services IRB members is presented in Appendix 16.1.3.

The March 28, 2002 protocol and informed consent document were approved by the MDS Pharma Services IRB on April 9, 2002. The April 11, 2002, revisions and certifications of translation from English to Spanish to the informed consent document, were approved by the MDS Pharma Services IRB on April 15, 2002.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki, and other principles of the ICH Good Clinical Practice Guideline[1, 2].

5.3 Subject Information and Consent

Prior to study enrollment the study specific informed consent (Elan Pharmaceuticals, Inc. ELN151607-105) was reviewed with the subject emphasizing the nature of the study, the drug product tested, potential adverse events, conduct of the study, and dates of confinement and ambulatory procedures. (Appendix 16.1.3). All subjects gave written informed consent to participate in the Elan Pharmaceuticals, Inc. ELN151607-105 study and were allowed to ask and have answered questions concerning the conduct of the study prior to enrollment in the study.

6.0 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

Clinical Research Investigators and Facilities:

Mark J. Allison, M.D., Principal Investigator (Appendix 16.1.4 and Appendix 16.1.5)
Irving E. Weston, M.D., Sub- Investigator (Appendix 16.1.4)

MDS Pharma Services
Phoenix , AZ 85040

Activities: Study management, on-site protocol activities, dosing, and sample collection, physical examination, medical record review and medical investigator on-site and on-call professional services

Clinical Laboratory Facilities:

Robert A. Earl, Ph.D.
MDS Pharma Services
Lincoln, NE 68516

[Hematology, Chemistry Urinalysis, Drug Screen, Pregnancy Hepatitis B surface antigen, Hepatitis C antibody, HIV antibody]

Activities: Certified reference clinical laboratories, clinical lab sample analysis

Analytical Investigator & Facility:

Gary Erdmann, Ph.D.
PRACS Institute, Ltd.
Fargo, ND 58104

Activities: Responsible for bioanalytical analyses.

Statistical Analysis:

Brenda L. Krogen, M.S.
PRACS Institute, Ltd.
Fargo, ND 58104

Activities: Responsible for pharmacokinetic and statistical analyses.

7.0 INTRODUCTION

Metaxalone is a central nervous system depressant that has sedative and skeletal muscle relaxant effects. Metaxalone is indicated as an adjunct to rest, physical therapy and other measures for the relief of discomforts associated with acute, painful musculoskeletal conditions[3]. The recommended dose for adults and children over 12 years of age is two tablets (400 mg per tablet, 800 mg total dose) three to four times a day.[3]

The mechanism of action of metaxalone in humans has not been established, but may be due to general central nervous system depression. It has no direct action on the contractile mechanism of striated muscle, the motor end plate, or the nerve fiber.[3]

Metaxalone is metabolized by the liver.[4] Precautions include the following: metaxalone must be administered with great care to patients with pre-existing liver damage; false positive Benedict's tests due to an unknown reducing substance have been noted; safe use has not been established with regard to possible adverse effects upon fetal development; it is unknown whether it is secreted in human milk, and the safety and effectiveness in children 12 years of age and below has not been established.

In the elderly, reduction in the metabolic capacity of the liver is commonly seen.[5] This is often the result of a reduction in hepatic blood flow as well as a reduction in hepatic mass and volume.[6-7] Further, there are pharmacokinetic changes associated with aging. There can be altered responsiveness to the absorption, distribution, metabolism and excretion of drugs.[6, 8] This is often the result of altered physiology.[6] For example, the apparent Vd of lipid soluble drugs can be raised due to changes (usually increase) in fat-to-lean body composition ratio.[7-8] The alteration (decrease) in renal blood flow can also greatly impact the excretion of drugs.[6-7] Drug toxicity caused by increased free drug levels due to impaired drug protein binding or displacement from protein binding sites can be seen.[6]

The most frequent reactions to metaxalone include nausea, vomiting, gastrointestinal upset, drowsiness, dizziness, headache, and nervousness or "irritability". Other adverse events are hypersensitivity reaction, characterized by a light rash with or without pruritis; leukopenia, hemolytic anemia; and jaundice.

8.0 STUDY OBJECTIVE

The primary objectives are to evaluate the effect of age and food on the pharmacokinetics of Skelaxin® (metaxalone) when administered to young and elderly age groups.

9.0 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was single center, open label, single dose, two-period (per each age group), randomized, two way crossover trial in healthy subjects between the ages of 18-55 years old (young) and the elderly (65 and older); treatments were follows:

Treatment A: Skelaxin® (metaxalone) tablet 2 x 400 mg tablet administered with food
Treatment B: Skelaxin® (metaxalone) tablet 2 x 400 mg tablet administered without food

A standardized breakfast was given to the subjects 45 minutes prior to dosing and was consumed within a 30 minute period. The dose of study drug was administered to the subjects 15 minutes after the breakfast was finished.

The breakfast consisted of the following:

2 eggs (fried in butter)
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
1 glass whole milk (8 ounces)

Nineteen blood samples were collected, starting with baseline (0 hour) and at the following time points: 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36, and 48 hours. In Period II, a blood sample at approximately 168 hours was collected to ensure the study drug was eliminated from the body.

A total of 48 subjects (24 males and 24 females) were enrolled. Forty-four of 48 subjects completed both treatments and the plasma samples were assayed and used in the pharmacokinetic analysis. Four subjects completed only one treatment and were not used in the pharmacokinetic analysis.

9.2 Discussion of Study Design

This was a single center, open label, single dose, two-period (per each age group), randomized, two way crossover trial in healthy subjects, between the ages of 18-55 years old (young) and the elderly (65 and older).

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

- Agreed to participate voluntarily and signed and dated an IRB-approved written, subject informed consent form;
- At least 18 years old at the time of screening ;
- Within ± 20% of ideal body weight according to the Metropolitan Height and Weight Tables;
- Female subjects of childbearing potential were not pregnant or lactating and were willing to use a medically appropriate form of contraception for the duration of the study.

9.3.2 Exclusion Criteria

- Not competent to provide informed consent;
- Displays clinically significant abnormalities on screening evaluations which consist of: physical examination, heart rate and sitting (1 minute) blood pressure, temperature, 12 lead ECG, and clinical laboratory tests. Deviations from the established normal ranges may be acceptable for study participation if, in the opinion of the investigator and Sponsor, they are not clinically meaningful or are viewed as normal for that individual. Individual screening tests may be repeated by the investigator to confirm accuracy of the original determinations or to further evaluate the clinical significance of deviations;
- Clinically significant illness within 4 weeks of screening;
- Known to be HIV positive, hepatitis B antigen positive, or hepatitis C antibody positive;
- History of drug or alcohol addiction or abuse;
- Use of tobacco products within the last 6 months;
- Use of any drugs including food supplements, herbal remedies and non-prescribed drugs known to induce or inhibit hepatic drug metabolism within 30 days prior to screening as listed in Appendix A of the protocol (Appendix 16.1.1);

- History of clinically significant drug allergies or allergic responses to metaxalone or related drugs;
- Females who are pregnant or breastfeeding;
- Blood donation within 30 days of screening or plasma donation within 14 days of screening;
- Participation in a clinical trial of an investigational drug or device within 30 days of the treatment phase;
- Considered by the investigator to be unsuitable for study participation, for any reason.

9.3.3 Removal of Subjects from Therapy or Assessment

Subjects could have been discontinued or withdrawn from the study for any of the following reasons:

- At the subject's request
- At the discretion of the investigator, if deemed appropriate, for any reason
- At the discretion of the Sponsor, if deemed appropriate, for any reason

Four subjects, subjects 29, 33, 34, and 45 were discontinued or withdrawn after Period I dosing.

9.4 Treatments

9.4.1 Treatments Administered

A single dose of Skelaxin® 400 mg tablet (2 x 400 mg) was administered to each subject according to the randomization scheme and according to the specific instructions for administration. The study drug was administered as follows:

Treatment A: 2 x 400mg Skelaxin® (metaxalone) with food
Treatment B: 2 x 400mg Skelaxin® (metaxalone) without food

Breakfast was given to the subjects approximately 45 minutes prior to dosing and consumed within a 30 minute period. The dose of study drug was administered to the subjects approximately 15 minutes after the breakfast was finished. The breakfast consisted of the following:

2 eggs (fried in butter)
2 strips of bacon
2 slices of toast with butter
4 ounces of hash brown potatoes
1 glass whole milk (8 ounces)

Subjects were sequentially dosed at 1 minute intervals. All forty-eight subjects received one dose of Skelaxin®. Dosing was completed as scheduled in 44 of 48 subjects.

The following subjects did not receive a second dose of Skelaxin® Subject 29 was dropped for elevated ALT and Subject 33 was dropped for anemia. Subject 34 did not return for Period II check-in, and Subject 45 was dropped on Day 3 of Period I due to non-compliance.

Under the investigator's direction, an accurate dispensing log was maintained to record dates and amount of medication dispensed to each subject in the trial. In addition, an entry on the case report form for each subject provides a record of this activity.

All unused study product is accounted for and was returned to Elan Biopharmaceuticals.

Subjects were continuously monitored by MDS Pharma Services staff throughout the confinement portion of the study.

9.4.2 Identity of Investigational Product

Name:	Skelaxin®
Substance:	Metaxalone
Dosage Form:	Tablet
Content:	400 mg
Route:	Oral
Batch/Lot No.:	34851A
Expiration Date:	31-Jan-05
Manufacturer:	Mallinckrodt Hobart

9.4.3 Method of Assigning Subjects to Treatment Group

All subjects received 2 tablets of Skelaxin® (metaxalone) 400 mg. The randomization schedule is located in Appendix 16.1.6.

9.4.4 Selection of Doses in the Study

The dose selected (2 x 400 mg Skelaxin®) is the recommended dose for this product.

9.4.5 Selection and Timing of Dose for Each Subject

Subjects were sequentially dosed at 1 minute intervals under fasting or fed conditions, dependent on randomization.

Food was restricted 10 hours pre-dose until 4 hours post-dose (fasting group).

9.4.6 Blinding

Not Applicable

9.4.7 Prior and Concomitant Therapy

The investigator's staff obtained information about concomitant illnesses and therapeutic interventions. The investigator's staff recorded the dates of onset and remission of all symptoms and diagnosed conditions, as well as the name, daily dose and dates of self medications.

9.4.8 Treatment Compliance

At admission to the clinical research facility, all subjects were questioned regarding their compliance to the protocol since their previous visit. Subjects were continuously monitored by MDS Pharma Services staff throughout the confinement portion of the study.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and Safety Measurements Assessed and Flow Chart

Efficacy was not an objective of the study design. Safety measurements performed over the course of the study were as follows:

1. A medical history and a physical examination were performed at the screening visit and at the post-study visit.
2. Vital signs (sitting (1 minute)) blood pressure, pulse, and oral temperature) were measured at all visits and on the PK profile days at pre-dose and approximately 2, 6, 12, and 24 hours post dose.

3. Clinical laboratory tests, including a serum pregnancy screen (females only), were performed at screening and on Days -1, 7, and at the post-study visit.
4. A 12 lead ECG was performed at the screening and post-study visits.
5. Adverse events were recorded.

SCHEDULE OF EVENTS

	Screen	Treatment Period 1			Wash-out	Treatment Penod 2			Post study
Procedure	Day −14 to -1	Day – 1 Over-night	1 Over-night	2-3	2-6 Wash-out	7-Over-night	8-Over-night	9-10	
Informed consent	X								
Inclusion/ Exclusion	X	X							
Medical history	X								
Physical exam	X								X
Vital signs	X	X	X[1]	X		X	X[1]	X	X
12 lead ECG	X								X
Fast overnight (10 hours)		X				X			
Hematology, chemistry, unnalysis	X	X				X			X
Serum Pregnancy	X	X				X			X
Drug/alcohol screen	X	X				X			
PK samples			X[2]				X[2]		X
Breakfast (For treatment A only)			X				X		
Study drug administration			X				X		
Adverse events			X	X		X	X	X	X
Concomitant medication	X	X		X		X		X	X

[1]Obtain vital signs pre-dose and 2, 6, 12 and 24 hours post-study drug administration
[2]Obtain PK samples at pre-dose, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36 and 48 hours post-dose.

9.5.2 Appropriateness of Measurements

The measurements performed are standard procedures for the conduct of pharmacokinetic studies.

9.5.3 Drug Concentration Measurements

Blood samples for the measurement of metaxalone plasma concentrations were collected at the following time points:

- Baseline (0 hour) (10 mL blood sample)
- 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36, and 48 hours after drug administration (1 x 10 mL blood sample).

The total blood volume taken per subject for pharmacokinetic analysis and clinical laboratory testing was approximately 444 mL for male subjects and 480 for female subjects over a period of approximately 30 days.

Samples were collected and stored in an ice bath. Plasma samples were separated by centrifugation, frozen at approximately -20°C, and kept frozen, packed in dry ice, and sent to PRACS Institute, Ltd., in Fargo, North Dakota.

9.6 Data Quality Assurance

All parts of the clinical phase of the study and all documentation were subject to inspection by Elan's independent quality assurance (QA) unit. Non-clinical (analytical) parts of the study were also subject to QA audit.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and Analysis Plans

For each age and treatment group, descriptive statistics of plasma concentrations at each sampling time was reported. Descriptive statistics for the pharmacokinetic parameters were presented by age and treatment group, as well. The age, treatment, and age-by-treatment effects for each pharmacokinetic parameter were tested using an ANOVA model with age, subject within age, treatment, and the age-by-treatment interaction as factors.

9.7.2 Determination of Sample Size

This was a descriptive study to determine the pharmacokinetics of 2 x 400 mg Skelaxin®(metaxalone) tablets when administered to volunteers between the ages of 18-55 and in volunteers 65 years of age and older in both the fed and fasted state. Due to the descriptive nature of the study, no power calculation was performed.

9.8 Changes in the Conduct of the Study or Planned Analyses

No changes were made during the conduct of the study or with the planned analyses that could have altered the study outcomes.

10. STUDY SUBJECTS

10.1 Disposition of Subjects

The study was successfully completed by 44 of 48 subjects enrolled. At enrollment, all 48 subjects met study inclusion and exclusion criteria as documented by an acceptable medical history, medication history, physical examination, sitting blood pressure, heart rate, electrocardiogram, clinical laboratory evaluations, a non-reactive HIV antibody screen, and negative screens for Hepatitis B surface antigen, Hepatitis C antibody, pregnancy (females only), and drugs of abuse fourteen days prior to Period I dose administration. All female subjects had a negative pregnancy screen prior to dose administration. All subjects gave written informed consent and were allowed to ask and have answered questions concerning the conduct of the study prior to enrollment in the study. The trial was conducted under medical supervision.

Tables 10.1.1, 10.1.2, and 10.1.3 summarize the demographic characteristics for young subjects, older subjects, and for both age groups combined.

Table 10.1.1: Subject Demographic
Descriptive Statistics for Young Subjects
(12 Young Males; 12 Young Females; 24 Young Subjects)

	Age			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Young Male	35.5 ± 13.4 years	18 years	34 years	55 years
Young Female	43.1 ± 5.6 years	37 years	42 years	54 years
Young All	39.3 ± 10.8 years	18 years	40 years	55 years

	Weight			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Young Male	179.2 ± 15.5 lbs.	148 lbs.	175.0 lbs.	205 lbs
Young Female	137.8 ± 15.4 lbs.	116 lbs.	142.5 lbs.	171 lbs.
Young All	158.5 ± 26.0 lbs	116 lbs.	155.0 lbs.	205 lbs

	Height			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Young Male	70.8 ± 2.9 in.	66.5 in.	66.8 in.	75.0 in.
Young Female	64.2 ± 2.1 in.	60.5 in.	64.0 in.	67.0 in.
Young All	67.5 ± 4.2 in.	60.5 in.	67.0 in	75.0 in.

Data Source: Appendix 16.2.4

Table 10.1.2: Subject Demographic
Descriptive Statistics for 65 and Older Subjects
(12 Older Males; 12 Older Females; 24 Older Subjects)

	Age			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Elderly Male	71.4 ± 4.5 years	66 years	71 years	81 years
Elderly Female	71.5 ± 5.7 years	65 years	70 years	81 years
Elderly All	71.5 ± 5 years	65 years	70 years	81 years

	Weight			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Elderly Male	173.7 ± 24.6 lbs.	116 lbs.	180.0 lbs.	204 lbs
Elderly Female	141.3 ± 21.9 lbs.	112 lbs.	138.0 lbs.	185 lbs.
Elderly All	157.5 ± 28.1 lbs.	112 lbs.	159.0 lbs	204 lbs

	Height			
	Mean ± Standard Deviation	Minimum	Median	Maximum
Elderly Male	69.3 ± 1.9 in.	66.0 in.	69.0 in.	72.0 in.
Elderly Female	64.4 ± 3.2 in	60.5 in	64.0 in	70.5 in
Elderly All	66.8 ± 3.6 in.	60.5 in	67.5 in	72.0 in.

Data Source. Appendix 16.2.4

Table 10.1.3: Subject Demographic Descriptive Statistics for All Subjects (24 Males; 24 Females; 48 Subjects Total)

	Age			
	Mean ± Standard Deviation	Minimum	Median	Maximum
All Males	53.5 ± 20.8 years	18 years	61 years	81 years
All Females	57.3 ± 15.5 years	37 years	60 years	81 years
All Subjects	55.4 ± 18.3 years	18 years	60 years	81 years

	Weight			
	Mean ± Standard Deviation	Minimum	Median	Maximum
All Males	176.4 ± 20.3 lbs.	116 lbs.	158.5 lbs.	205 lbs
All Females	139.5± 18.6 lbs	112 lbs.	142.0 lbs.	185 lbs.
All Subjects	158 ± 26.8 lbs.	112 lbs.	145.0 lbs.	205 lbs.

	Height			
	Mean ± Standard Deviation	Minimum	Median	Maximum
All Males	70 ± 2.5 in.	66.0 in.	70.3 in.	75.0 in.
All Females	64.3 ± 2.6 in.	60.5 in.	64.0 in.	70.5 in.
All Subjects	67.1 ± 3.9 in.	60.5 in.	65.0 in.	75.0 in.

Data Source: Appendix 16.2.4

The weight of the volunteers was not more than ± 20% of the ideal for height and body frame as per the Desirable Weights for Men or the Desirable Weights for Women – Metropolitan Height and Weight Table.

Appendix 16.2.4 includes a table presenting the demographic data for all 48 subjects enrolled in the study.

10.2 Protocol Deviations

The following protocol deviations occurred during the conduct of this study:

Sub. No.	Deviation
45	According to the protocol, post-study events were to include the following: vital signs, a physical exam, clinical laboratory tests, and an ECG. Subject's early termination events were all completed prior to release except for an ECG.
31	According to the protocol, a blood sample was to be obtained at 4.5 hours post-dose. During Period 1, the 4.5-hour sample was not obtained due to a difficult venipuncture.
31	According to the protocol, a blood sample was to be obtained at 1.5 hours post-dose. During Period 2, the 1.5-hour sample was not obtained due to a difficult venipuncture.
27	According to the protocol, a blood sample was to be obtained at 3.5 and 4.5 hours post-dose. During Period 2, the 3.5 and 4.5 hour samples were not obtained due to difficult venipuncture.

11. PHARMACOKINETIC AND PHARMACODYNAMIC PARAMETERS

11.1 Pharmacokinetics

The pharmacokinetic parameters were calculated using WinNonlin™, Version 3.1, software designed specifically for analyzing pharmacokinetic data. WinNonlin™ Model 200 for extravascular input was utilized. All other computations were completed using SAS®, Version 8.2 for Windows. Microsoft® Excel® 97 was used to produce tables and graphs.

The following pharmacokinetic parameters were computed from the plasma concentration data using the actual sample collection times:

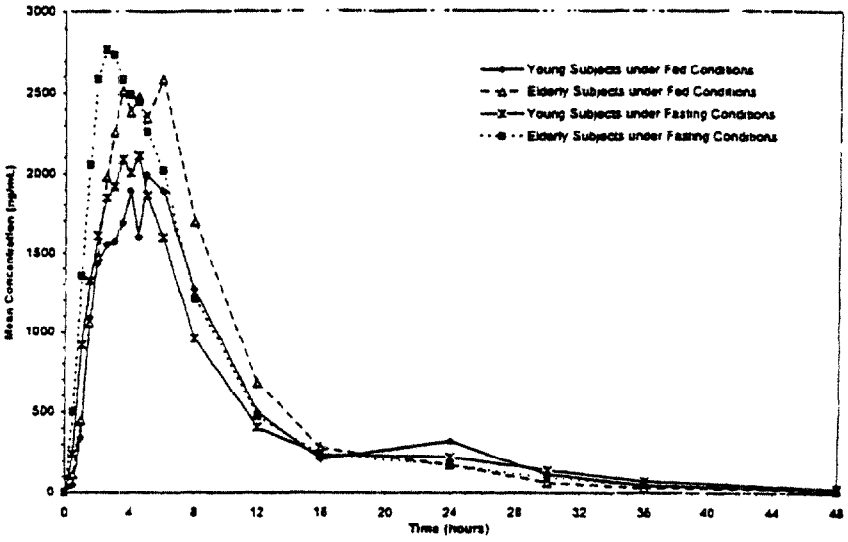
- T_{max}: Time to maximum concentration;
- C_{max}: Observed maximum concentration;
- k_{el}: Slope of terminal linear portion of concentration-time curve;
- $T_{1/2}$: Half-life of metaxalone calculated as: $0.693/K_{el}$;
- $AUC_{(last)}$: Area under the curve to last quantifiable concentration as measured by the trapezoidal rule;
- $AUC_{(inf)}$: The AUC value extrapolated to infinity calculated as: $AUC_{(inf)} = AUC_{(last)} + C(t)last/K_{el}$ where C(t)last is the last measurable concentration.

Natural logarithmic (ln) transformations were computed for $AUC_{(last)}$, $AUC_{(inf)}$ and C_{max} and were employed for the statistical analysis. An analysis of variance (ANOVA) was performed on each of the following pharmacokinetic parameters using SAS® software: non-transformed T_{max}, C_{max}, k_{el}, $T_{1/2}$, $AUC_{(last)}$, and $AUC_{(inf)}$; and ln-transformed $AUC_{(last)}$, $AUC_{(inf)}$, and C_{max}. ANOVA models included factors for age, subjects within age, treatment, and the treatment-by-age interaction were utilized in comparing the age, treatment and age-by-treatment effects. Effects were declared statistically significant at the 5% level of significance.

The lower limit of quantitation for metaxalone was 10 ng/mL. For statistical analysis, subject sample values below the lower limit of quantitation (BLQ) were reported as zero.

Figure 11.1.1 illustrates the mean plasma concentration curves by treatment and age from time 0 to 48 hours after dosing on a linear scale.

Figure 11.1.1: Mean Plasma Concentration (0 - 48 hours)



The mean plasma concentration curves appear to be somewhat different between young and elderly subjects and between fed and fasted conditions in each of the two age groups. However, the differences do not appear to be substantial.

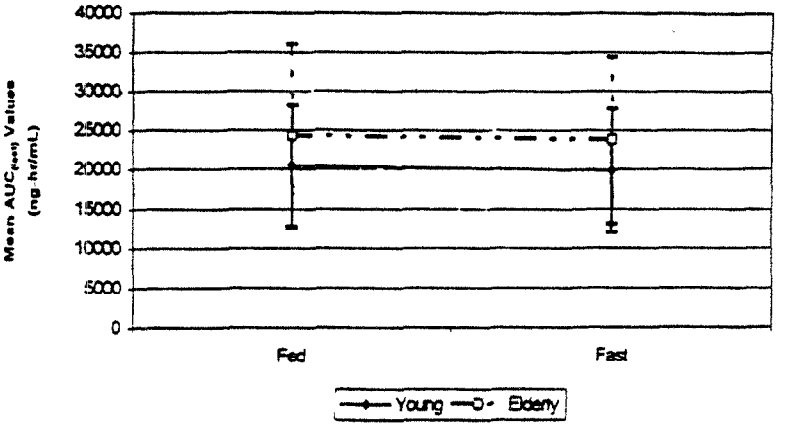
Tables 11.1.1 – 11.1.3 present descriptive statistics (arithmetic mean and coefficient of variation) by age and treatment groups for $AUC_{(last)}$, $AUC_{(inf)}$, and C_{max}, respectively. Figures 11.1.2 – 11.1.4 display the arithmetic mean plus or minus the standard deviation by age and treatment groups for $AUC_{(last)}$, $AUC_{(inf)}$, and C_{max}, respectively.

Table 11.1.1: Mean and Coefficient of Variation for $AUC_{(last)}$ (ng-hr/mL) Skelaxin® (metaxalone) when Administered With and Without Food

	Administered With Food	Administered Without Food
Young Subjects (N=21)	20482.38 ng-hr/mL (37.33%)	19836.24 ng-hr/mL (39.52%)
Elderly Subjects (N=23)	24340.43 ng-hr/mL (48.01%)	23797.04 ng-hr/mL (44.64%)

Data Source: Appendix 16.2.5.5 – 16.2.5.8

Figure 11.1.2: Mean +/- Standard Deviation by Age Group and Treatment Group for $AUC_{(last)}$



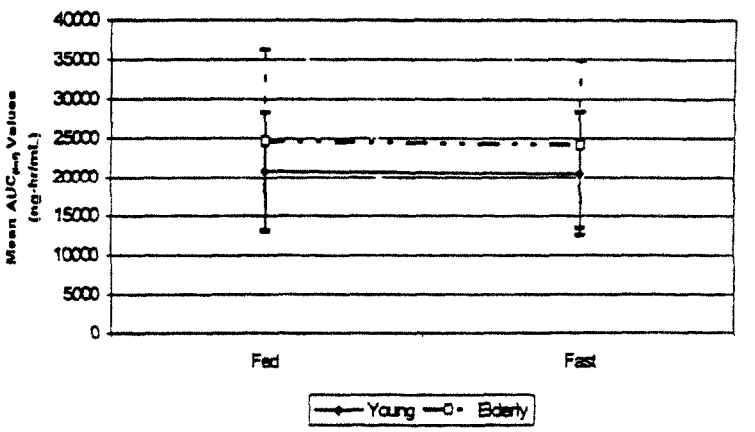
Based on Table 11.1.1 and Figure 11.1.2, there appears to be a slight age effect since the mean $AUC_{(last)}$ values are slightly greater for the elderly subjects when compared to the young subjects for either treatment. There appears to be at most a small treatment effect given the amount of change in the mean $AUC_{(last)}$ values between fed to fasting treatments for either age group.

Table 11.1.2: Mean and Coefficient of Variation for $AUC_{(inf)}$ (ng-hr/mL) Skelaxin® (metaxalone) when Administered With and Without Food

	Administered With Food	Administered Without Food
Young Subjects (N=21)	20814.57 ng-hr/mL (36.46%)	20489.57 ng-hr/mL (38.61%)
Elderly Subjects (N=23)	24704.17 ng-hr/mL (47.21%)	24194.13 ng-hr/mL (44.18%)

Data Source: Appendix 16.2.5.5 – 16.2.5.8

Figure 11.1.3: Mean +/- Standard Deviation by Age Group and Treatment Group for $AUC_{(inf)}$



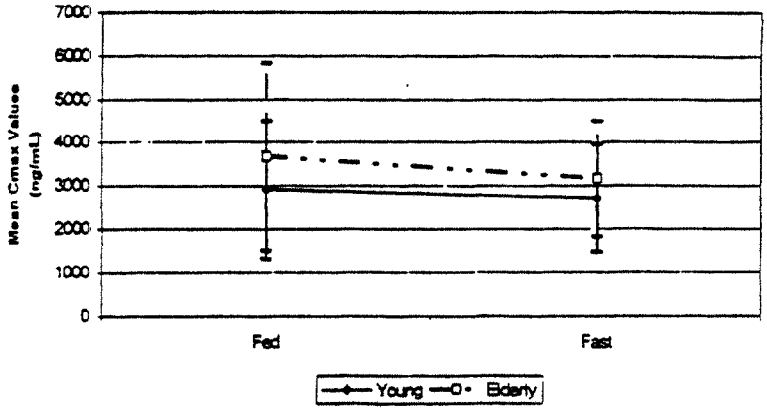
Based on Table 11.1.2 and Figure 11.1.3 there appears to be a slight age effect since the mean $AUC_{(inf)}$ values are slightly greater for the elderly subjects when compared to the young subjects for either treatment. There appears to be at most a small treatment effect given the amount of change in the mean $AUC_{(inf)}$ values from fed to fasting treatments for either age group.

Table 11.1.3: Mean and Coefficient of Variation for C_{max} (ng/mL) Skelaxin® (metaxalone) when Administered With and Without Food

	Administered With Food	Administered Without Food
Young Subjects (N=21)	2915.27 ng/mL (54.60%)	2719.02 ng/mL (45.51%)
Elderly Subjects (N=23)	3680.21 ng/mL (58.74%)	3167.89 ng/mL (42.46%)

Data Source: Appendix 16.2.5.5 – 16.2.5.8

Figure 11.1.4: Mean +/- Standard Deviation by Age Group and Treatment Group for C_{max}



Based on Table 11.1.3 and Figure 11.1.4, there appears to be a slight age effect since the mean C_{max} values are slightly greater for the elderly subjects when compared to the young subjects for either treatment. There appears to be at most a small treatment effect given the amount of change between the mean C_{max} values for fed and fasting treatments for either age group.

Table 11.1.4 summarizes the statistical results for age, treatment, and interaction (age-by-treatment) effects for $AUC_{(last)}$, $AUC_{(inf)}$, and C_{max}. There were no statistically significant age, treatment, or age-by-treatment interaction effects detected for any of the ln-transformed pharmacokinetic parameters.

Table 11.1.4: Summary of Statistical Results

P-Values	Ln-Transformed Data		
	$AUC_{(last)}$ (ng-hr/mL)	$AUC_{(inf)}$ (ng-hr/mL)	C_{max} (ng/mL)
Age Effect	0.3589	0.3891	0.2037
Treatment Effect	0.4353	0.5618	0.6988
Interaction Effect	0.3986	0.4935	0.9600

Data Source: Appendix 16.2.5, pp. 349 - 351

Table 11.1.5 presents the median and range for T_{max} by age and treatment groups.

Table 11.1.5: Median and Range for T_{max} (hr)
Skelaxin® (metaxalone) when Administered With and Without Food

	Administered With Food	Administered Without Food
Young Subjects (N=21)	6.00 hr (2.00 hr to 24.00 hr)	2.53 hr (1.00 hr to 5.00 hr)
Elderly Subjects (N=23)	6.00 hr (2.50 hr to 24.00 hr)	2.50 hr (1.00 hr to 4.53 hr)

Data Source: Appendix 16.2.5.5 – 16.2.5.8

Appendix 16.2.5 contains the plasma concentration levels and pharmacokinetic parameters by age and treatment. The overlay graphs as well as the individual graphs are also included.

12. SAFETY EVALUATION

12.1 Extent of Exposure

The drug product received from Elan Pharmaceuticals, Inc. was as follows:

Skelaxin® 400 mg Tablets - 1 Bottle of 499 tablets by
Mallinckrodt Hobart;
Lot No. 34851A; Exp. Date: 31-Jan-05

All subjects received the study product (Skelaxin® 400 mg tablet) administered with and without food, dependent on randomization scheme.

12.2 Adverse Events

12.2.1 Brief Summary of Adverse Events

During the study, adverse events were mild in severity and no serious or severe adverse events were reported. A total of 54 adverse events were reported by 25 of 48 subjects enrolled. Thirty-one of the adverse events reported were considered related to the study drug. The most frequently reported adverse event was headache (Tables 14.1.1.1 – 14.1.1.4)

12.2.2 Display of Adverse Events

Adverse events are listed in tables by age group and treatment group in Tables 14.1.1.1 – 14.1.1.4.

12.2.3 Analysis of Adverse Events

Of the 54 reported adverse events, 31 were considered related to study medication. In the opinion of the investigators, the other 23 adverse events were unrelated to study medication. None of the adverse events were considered serious.

12.2.4 Listing of Adverse Events by Subject

All adverse events are listed in Appendix 16.2.6.

12.3 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

No deaths, other serious adverse events, or other significant adverse events occurred.

12.4 Clinical Laboratory Evaluation

12.4.1 Evaluation of Each Laboratory Parameter

Refer to Appendix 16.2.7.1 – 16.2.7.6 for individual laboratory listings for the following tests: Hematology, Chemistry, Urinalysis,

Drugs of Abuse, HEP B&C and Pregnancy Screens. There were no clinically significant changes in the clinical laboratory parameters over the course of the study. Due to the sensitivity associated with HIV tests, MDSPS prefers to keep results as secure as possible as it is not part of normal operations to release the results, unless requested by the client.

12.5 Vital Signs, Physical Findings, ECG, and Other Observations Related to Safety

No changes were noted from the screening to the post-study physical examinations that were considered clinically significant by the Medical Investigator. No clinically significant changes were noted from the screening to the post-study electrocardiogram. The blood pressure and heart rate values reported over the course of the study were considered 'normal' for a group of healthy subjects. (Appendix 16.4)

12.6 Safety Conclusions

The clinical portion of the project was completed without any significant sequelae attributable to the investigational drug. In general, all blood sample collections were successfully completed as per protocol design.

13. DISCUSSION AND OVERALL CONCLUSIONS

Age Effect
Elderly subjects had slightly higher values for $AUC_{(last)}$, $AUC_{(inf)}$, and C_{max}, when compared to the values for young subjects. These differences were not found to be statistically significant.

Food Effect
In the presence of food, the C_{max}, $AUC_{(last)}$, and $AUC_{(inf)}$ were increased in both age groups, although these differences did not reach statistical significance.

Safety
Fifty-four adverse events were reported by 25 subjects enrolled in this study. Thirty-one were considered to be drug related (57.4%). The most common drug-related adverse event reported was headache (10 reports, 32 .3%). The most adverse events were reported by elderly fed subjects (19 reports, 35.2%). All adverse events, however, were considered to be mild in nature. Further the investigator concluded that Skelaxin® is safe and well-tolerated.

Conclusions

- Age had no significant effect on any pharmacokinetic parameter measured.
- Skelaxin® was safe and well tolerated by the subjects.

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 Safety Data Summary Figures and Tables

14.1.1 Displays of Adverse Events

Table 14.1.1.1: Adverse Events (Count, Percent of Subjects, and Subject Identification) for Young Subjects under Fed Conditions (N=21)

Event	Mild		Moderate		Severe		Total		Total
	Related*	NR**	Related*	NR**	Related*	NR**	Related*	NR**	
Sweating increased	1 (4.8%) 9						1		1
Nausea	1 (4.8%) 9						1		1
Somnolence	2 (9.5%) 26, 36						2		2
Headache	2 (9.5%) 26, 35	2 (9.5%) 26, 32					2	2	4
Respiratory Disorder		1 (4.8%) 35						1	1

*Related to Study Drug (Likely, Probably, or Possibly)
**Not Related to Study Drug (Unlikely or Unrelated)
(%) Denotes the percent of total subjects within age-by-treatment group
Refers to the subject study number

Data Source: Appendix 16.2.6.1

Table 14.1.1.2: Adverse Events (Count, Percent of Subjects, and Subject Identification) for Elderly Subjects under Fed Conditions (N=23)

Event	Mild		Moderate		Severe		Total		Total
	Related*	NR**	Related*	NR**	Related*	NR**	Related*	NR**	
Somnolence	4 (17.4%) 17, 23, 38, 42						4		4
Dizziness	2 (8.7%) 37, 39	1 (4.3%) 41					2	1	3
Headache	5 (21.7%) 37, 39, 40, 41, 48						5		5
Abdominal Pain	1 (4.3%) 39						1		1
Fatigue	2 (8.7%) 40, 45						2		2
Pain		2 (8.7%) 43, 45						2	2
Concentration Impaired	1 (4.3%) 45						1		1

*Related to Study Drug (Likely, Probably, or Possibly)
**Not Related to Study Drug (Unlikely or Unrelated)
(%) Denotes the percent of total subjects within age-by-treatment group.
Refers to the subject study number

Data Source: Appendix 16.2.6.1

Table 14.1.1.3: Adverse Events (Count, Percent of Subjects, and Subject Identification) for Young Subjects under Fasting Conditions (N=21)

Event	Mild		Moderate		Severe		Total		Total
	Related*	NR**	Related*	NR**	Related*	NR**	Related*	NR**	
Tooth Disorder				1 (4.8%) 7				1	1
Somnolence	2 (9.5%) 11, 25						2		2
Hypoesthesia		1 (4.8%) 31						1	1
Headache	1 (4.8%) 34	3 (14.3%) 2, 32, 34					1	3	4
Nausea	1 (4.8%) 34	1 (4.8%) 34					1	1	2
Respiratory Disorder		1 (4.8%) 34						1	1
Hot Flushes		1 (4.8%) 34						1	1

*Related to Study Drug (Likely, Probably, or Possibly)
**Not Related to Study Drug (Unlikely or Unrelated)
(%) Denotes the percent of total subjects within age-by-treatment group
Refers to the subject study number

Data Source: Appendix 16.2.6.1

Table 14.1.1.4: Adverse Events (Count, Percent of Subjects, and Subject Identification) for Elderly Subjects under Fasting Conditions (N=23)

Event	Mild		Moderate		Severe		Total		Total
	Related*	NR**	Related*	NR**	Related*	NR**	Related*	NR**	
Taste Perversion	1 (4.3%) 15						1		1
Somnolence	1 (4.3%) 39	2 (8.7%) 41, 41					1	2	3
Headache	2 (8.7%) 39, 48	2 (8.7%) 41, 46					2	2	4
Fatigue		2 (8.7%) 41, 41						2	2
Pain		1 (4.3%) 43						1	1
Dizziness	1 (4.3%) 46						1		1
Back Pain		2 (8.7%) 46, 47						2	2
Dyspepsia	1 (4.3%) 48						1		1

*Related to Study Drug (Likely, Probably, or Possibly)
**Not Related to Study Drug (Unlikely or Unrelated)
(%) Denotes the percent of total subjects within age-by-treatment group
Refers to the subject study number

Data Source Appendix 16.2.6.1

14.1.2 Listings of Deaths, Other Serious and Significant Adverse Events

There were no deaths, or other serious and/or significant adverse events in this study.

14.1.3 Narratives of Deaths, Other Serious and Certain Other Significant Adverse Events

There were no deaths, or other serious and/or certain other significant adverse events in this study.

14.1.4 Abnormal Laboratory Values

Table 14.1.4.1: Listing of Abnormal Hematology Laboratory Values at Screening by Subject

The following hematology laboratory test results were outside the reference range at screening. The results were deemed not clinically significant by the medical investigator, and subject enrollment was allowed

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
19	WBC	10.6	3.2 – 9.8 Thou/uL
30	HCT	43.9	31.9 – 43.6%
30	HGB	14.8	10.9 – 14.6% g/dL
31	HCT	45.7	31.9 – 43.6%
31	HGB	15.3	10.9 – 14.6 g/dL
31	RBC	5.06	3.5 – 5.05 Mil/uL
33	HGB	10.8	10.9 – 14.6 g/dL
36	HCT	44.1	31.9 – 43.6%
36	RBC	5.26	3.5 – 5.05 Mil/uL
39	HCT	45.5	31.9 – 43.6%
39	HGB	15.2	10.9 – 14.6 g/dL
41	HCT	44.5	31.9 – 43.6%
41	HGB	15.2	10.9 – 14.6 g/dL
41	Platelet Count	438	120 – 425 Thou/uL
42	HGB	15	10.9 – 14.6 g/dL
43	HCT	45.8	31.9 – 43.6%
43	HGB	15.2	10.9 – 14.6 g/dL
44	HCT	45	31.9 – 43.6%
44	HGB	15	10.9 – 14.6 g/dL
45	HCT	45.7	31.9 – 43.6%
45	HGB	15.3	10.9 – 14.6 g/dL
45	RBC	5.1	3.5 – 5.05 Mil/uL
48	HCT	46.3	31.9 – 43.6%
48	HGB	15.1	10.9 – 14.6g/dL
48	RBC	5.15	3.5 – 5.05 Mil/uL

Data Source: Appendix 16.2.7.1

Table 14.1.4.2: Listing of Abnormal Hematology Laboratory Values During Study Period I by Subject

The following Period I check-in hematology laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
22	WBC	10.1	3.2 – 9.8 Thou/uL
29	WBC	10.4	3.2 – 9.8 Thou/uL
33	HGB	10.7	10.9 – 14.6 g/dL
39	HGB	14.9	10.9 – 14.6 g/dL
41	HCT	44.2	31.9 – 43.6%
41	HGB	15	10.9 – 14.6 g/dL
41	Platelet Count	436	120 – 425 Thou/uL
42	HCT	43.7	31.9 – 43.6%
42	HGB	14.7	10.9 – 14.6 g/dL
42	WBC	10.7	3.2 – 9.8 Thou/uL
43	HCT	44.4	31.9 – 43.6%
43	HGB	14.9	10.9 – 14.6 g/dL
45	HGB	14.9	10.9 – 14.6 g/dL
48	HCT	46.8	31.9 – 43.6%
48	HGB	15.6	10.9 – 14.6 g/dL
48	RBC	5.18	3.5 – 5.05 Mil/uL

Data Source. Appendix 16.2.7.1

Table 14.1.4.3: Listing of Abnormal Hematology Laboratory Values During Study Period II by Subject

The following Period II check-in hematology laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
12	WBC	10.3	3.2 – 9.8 Thou/uL
13	HCT	36.9	37.2 – 50.2%
13	RBC	3.65	4 – 5.70 Mil/uL
18	RBC	3.79	4 – 5.70 Mil/uL
25	Platelet Count	434	120 – 425 Thou/uL
29	WBC	10.3	3.2 – 9.8 Thou/uL
33	HCT	31.7	31.9 – 43.6%
33	HGB	10.1	10.9 – 14.6 g/dL
42	WBC	11	3.2 – 9.8 Thou/uL

Data Source: Appendix 16.2.7.1

Table 14.1.4.4: Listing of Abnormal Hematology Laboratory Values at Study Exit by Subject

The following hematology laboratory test results were outside the reference range at study exit. The results were deemed not clinically significant by the medical investigator, and no repeat measurements were requested.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
13	RBC	3.87	4 – 5.7 Mil/uL
18	RBC	3.97	4 – 5.7 Mil/uL
19	WBC	11.1	3.2 – 9.8 Thou/uL
25	Platelet Count	465	120 – 425Thou/uL
33	HGB	10.6	10.9 – 14.6 g/dL
35	HGB	10.8	10.9 – 14.6 g/dL
45	HCT	47	31.9 – 43.6%
45	HGB	15.9	10.9 – 14.6 g/dL
45	RBC	5.2	3.5 – 5.05 Mil/uL
48	HCT	44.9	31.9 – 43.6%
48	HGB	14.9	10.9 – 14.6 g/dL

Data Source: Appendix 16.2.7.1

Table 14.1.4.5: Listing of Abnormal Chemistry Laboratory Values at Screening by Subject

The following screening clinical chemistry laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator. Subject enrollment was allowed.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
1	Uric Acid	8	2.7 – 7.8 mg/dL
3	Uric Acid	8.5	2.7 – 7.8 mg/dL
3	AST(GOT)	9	11 – 46 U/L
4	Creatinine	1.3	0.6 – 1.2 mg/dL
5	Total Bilirubin	1.3	0.1 – 1.1 mg/dL
7	Potassium	5.5	3.8 – 5 mEq/L
12	Total Bilirubin	1.3	0.1 – 1.1 mg/dL
14	Urea	21	8 – 20 mg/dL
15	LD (LDH)	217	116 – 213 U/L
15	Total Bilirubin	1.2	0.1 – 1.1 mg/dL
19	Urea	24	8 – 20 mg/dL
20	LD (LDH)	226	116 – 213 U/L
24	Urea	21	8 – 20 mg/dL
30	Total Protein	8.6	6.3 – 8 g/dL
32	Total Protein	8.3	6.3 – 8 g/dL

Table 14.1.4.5: Listing of Abnormal Chemistry Laboratory Values at Screening by Subject (cont'd)

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
36	Calcium	10.4	8 4 – 10.3 mg/dL
36	Total Protein	8.5	6.3 – 8 g/dL
37	LD (LDH)	227	116 – 213 U/L
41	Albumin	3.8	3.9 – 5.2 g/dL
43	Total Bilirubin	1.9	0.1 – 1.1 mg/dL
44	GGT	67	0 – 59 U/L
44	Total Protein	8.1	6.3 – 8 g/dL
46	Potassium	5.1	3.8 – 5 mEq/L

Data Source: Appendix 16.2.7.2

Table 14.1.4.6: Listing of Abnormal Chemistry Laboratory Values During Study Period I by Subject

The following Period I check-in clinical chemistry laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
1	Creatinine	1 4	0.6 – 1.2 mg/dL
1	Phosphorous	5.2	2 3 – 4.6 mg/dL
1	Total Protein	8.3	6.3 – 8.0 g/dL
2	Urea	21	8 – 20 mg/dL
3	Phosphorous	4.7	2.3 – 4.6 mg/dL
3	Uric Acid	8.8	2.7 – 7.8 mg/dL
4	Creatinine	1 4	0.6 – 1.2 mg/dL
4	Total Protein	8 4	6.3 – 8.0 g/dL
6	Urea	23	8 – 20 mg/dL
7	potassium	5.1	3.8 – 5 0 mEq/L
9	Phosphorous	5	2.3 – 4.6 mg/dL
12	Phosphorous	5	2.3 – 4.6 mg/dL
12	Total Bilirubin	1.7	0.1 – 1.1 mg/dL
12	Total Protein	8.2	6 3 – 8.0 g/dL
14	Urea	22	8 – 20 mg/dL
16	Creatinine	1.3	0.6 – 1.2 mg/dL
16	Urea	27	8 – 20 mg/dL
17	Creatinine	1 4	0.6 – 1.2 mg/dL
17	LD (LDH)	214	116 – 213 U/L
17	Urea	21	8 – 20 mg/dL
18	Total Protein	8 1	6.3 – 8.0 g/dL
18	Urea	23	8 – 20 mg/dL
19	Albumin	3 7	3.9 – 5.2 g/dL
19	Total Protein	6.2	6.3 – 8.0 g/dL
20	LD (LDH)	219	116 – 213 U/L
20	Urea	22	8 – 20 mg/dL
22	LD (LDH)	215	116 – 213 U/L
24	LD (LDH)	214	116 – 213 U/L
27	Total Protein	8 3	6.3 – 8.0 g/dL

Table 14.1.4.6: Listing of Abnormal Chemistry Laboratory Values During Study Period I by Subject (cont'd)

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
28	Total Protein	8.4	6.3 – 8.0 g/dL
30	Potassium	3.7	3.8 – 5.0 mEq/L
31	Urea	22	8 – 20 mg/dL
31	Uric Acid	2.6	2.7 – 7.8 mg/dL
32	Total Protein	8.2	6.3 – 8.0 g/dL
33	Uric Acid	2.4	2.7 – 7.8 mg/dL
34	Creatinine	0.5	0.6 – 1.2 mg/dL
34	Uric Acid	2.5	2.7 – 7.8 mg/dL
36	Carbon Dioxide	22	23 – 34 mmol/L
37	LD (LDH)	256	116 – 213 U/L
37	Total Protein	8.3	6.3 – 8.0 g/dL
37	Potassium	3.7	3.8 – 5.0 mEq/L
38	LD (LDH)	217	116 – 213 U/L
38	Urea	21	8 – 20 mg/dL
40	Phosphorous	4.7	2.3 – 4.6 mg/dL
42	Chloride	95	96 – 107 mEq/L
44	Total Protein	8.2	6.3 – 8.0 g/dL
46	Total Protein	8.1	6.3 – 8.0 g/dL
46	Urea	29	8 – 20 mg/dL
47	Urea	27	8 – 20 mg/dL

Data Source: Appendix 16.2.7.2

Table 14.1.4.7: Listing of Abnormal Chemistry Laboratory Values During Study Period II by Subject

The following Period II check-in clinical chemistry laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator.

Subject No	Laboratory Parameter	Laboratory Result	Reference Range
4	Creatinine	1 4	0.6 – 1.2 mg/dL
15	Magnesium	1.7	1 8 – 2 7mg/dL
19	Albumin	3.6	3.9 – 5.2 g/dL
19	AST (GOT)	55	11 – 46 U/L
19	Creatinine	1.3	0.6 – 1.2 mg/dL
20	Creatinine	1.4	0.6 – 1.2 mg/dL
20	LD (LDH)	245	116 – 213 U/L
24	LD (LDH)	221	116 – 213 U/L
27	Magnesium	1 7	1.8 – 2.7mg/dL
29	ALT (GPT)	71	0 – 50 U/L
29	AST (GOT)	55	11 – 46 U/L
29	GGT	76	0 – 59 U/L
33	Magnesium	1.7	1.8 – 2.7mg/dL
36	Phosphorous	4.8	2.3 – 4 6 mg/dL
37	LD (LDH)	237	116 – 213 U/L
43	LD (LDH)	218	116 – 213 U/L
44	potassium	3.7	3 8 – 5 mEq/L
47	Carbon Dioxide	22	23 – 34 mmol/L

Data Source: Appendix 16.2.7.2

Table 14.1.4.8: Listing of Abnormal Chemistry Laboratory Values at Study Exit by Subject

The following exit clinical chemistry laboratory test results were outside the reference range and deemed not clinically significant by the medical investigator. No repeat measurements were requested.

Subject No.	Laboratory Parameter	Laboratory Result	Reference Range
3	AST (GOT)	10	11 – 46 U/L
4	Albumin	3.8	3.9 – 5.2 g/dL
7	Total Protein	8.1	6.3 – 8.0 g/dL
7	Urea	7	8 – 20 mg/dL
12	Total Bilirubin	2.9	0.1 – 1.1 mg/dL
12	Total Protein	8.3	6.3 – 8.0 g/dL
18	Urea	21	8 – 20 mg/dL
19	Albumin	3.8	3.9 – 5.2 g/dL
19	ALT (GPT)	99	0 – 50 U/L
19	Urea	23	8 – 20 mg/dL
20	LD (LDH)	223	116 – 213 U/L
20	Urea	22	8 – 20 mg/dL
21	Phosphorous	2.2	2.3 – 4.6 mg/dL
21	Total Protein	8.1	6.3 – 8.0 g/dL
24	LD (LDH)	217	116 – 213 U/L
27	potassium	5.1	3.8 – 5.0 mEq/L
28	Total Protein	8.2	6.3 – 8.0 g/dL
30	Total Protein	8.4	6.3 – 8.0 g/dL
31	Total Protein	8.1	6.3 – 8.0 g/dL
32	Total Protein	8.5	6.3 – 8.0 g/dL
34	Albumin	3.8	3.9 – 5.2 g/dL
34	Uric Acid	2.2	2.7 – 7.8 mg/dL
36	Total Protein	8.5	6.3 – 8.0 g/dL
37	LD (LDH)	241	116 – 213 U/L
41	Albumin	3.7	3.9 – 5.2 g/dL
44	Total Protein	8.2	6.3 – 8.0 g/dL
46	Urea	22	8 – 20 mg/dL

Data Source: Appendix 16.2.7.2

The HIV antibody and hepatitis B surface antigen screen, and hepatitis C antibody were non-reactive and negative, respectively, for all subjects.

The screening, Period I and Period II check-in, and exit urinalysis values were unremarkable. The pregnancy screen at the screening visit, Period I and Period II check-in, and study exit was negative for all female subjects. The drug abuse screen at the screening visit, Period I and Period II check-in was negative for all subjects

There were no clinically significant changes in the clinical laboratory measurements over the course of the study, which could be reasonably associated with the formulations under investigation. All clinical laboratory values were reviewed by the medical investigator and follow-up completed as requested.

15. REFERENCE LIST

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16. APPENDICES – TABLE OF CONTENTS

16.3. Case Report Forms

16.3.1 Case Report Forms (for deaths, other serious adverse events, and withdrawals due to adverse events)

16.3.2 Other Case Report Forms

16.4 Individual Subject Data Listings